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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/340,595	06/28/1999	OSVALDO LUIS PODHAJCER	1581.0300002	4148

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EXAMINER
EPPS FORD, JANET L

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/340,595	PODHAJCER ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

2. Claims 55, and 58-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment of human melanoma tumors subcutaneously in humans and mice via administration o the SPARC antisense shown in the specification as filed, and methods of inhibiting SEQ ID NO:1, human SPARC, via administration of said antisense in cells in cell culture (*in vitro*), does not reasonably provide enablement for methods of administration of any SPARC inhibitor for any treatment as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record in the rejection of claims 15-17, 39-42 and 44-54 under 35 USC § 112 set forth in the Official Action mailed 3-10-2003.

3. Applicant's arguments filed 8-26-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification provides ample direction as to how to determine whether an antisense nucleic acid molecule decreases or prevents osteonectin expression, and that this decrease correlates to reduced tumorigenicity. Moreover, Applicants argue that it would be a matter of routine experimentation to identify antisense oligonucleotides for use in the practice of the claimed invention. Contrary to Applicant's assertions, in regards to the *in vivo* administration of antisense oligonucleotides

for the therapeutic treatment of a disease condition, neither the specification as filed nor the prior art provides sufficient guidance to the skilled artisan such that any antisense oligonucleotide targeting a osteonectin could be effectively used to reduce the size of a tumor in an animal, without undue experimentation.

The specification as filed provides only guidance for the subcutaneous injection of an antisense nucleic acid comprising a sequence that is the reverse complement of nucleotides 15 to 1689 of SPARC cDNA. There are no other examples that would suggest that the teachings of the specification as filed can be generally used for the effective administration of any other SPARC antisense nucleic acid molecule. Moreover, in regards to Applicant's examples, no direct effect of SPARC antisense transfected cells on parental cells was observed.

While the specification as filed is considered enabling for treatment of human melanoma tumors subcutaneously in humans and mice via administration of the SPARC antisense shown in the specification as filed, such results are not considered predictive nor enabling for treatment of other tumors, nor use of other inhibitors of SPARC (SEQ ID NO:1). As admitted by the specification and reiterated above, the role of SPARC/osteonectin is cell type specific and opposing results are found in the literature for the expected result of use of antisense versus sense expression in ovary cancer cells. Since there is no nexus taught in either the specification as filed or the prior art for how to administer SPARC antisense or other inhibitors to treat other types of tumors, one of skill in the art would necessarily practice *de novo* "trial and error" experimentation to discern the treatment potentials of other types of cancers.

In regards to Applicant's assertions that it would be a matter of routine experimentation to identify antisense oligonucleotides for use in the practice of the claimed invention, as stated in

the prior Office Action, there are multiple factors that contribute to the unpredictable behavior of antisense oligonucleotides in a whole organism. These factors are considered barriers to successful delivery of antisense oligonucleotide delivery in the organism: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetics profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming

the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. on page 79, col. 2.

Applicant's arguments do not take the place of evidence that the guidance in the specification as filed and the prior art are sufficiently clear such that one of skill in the art would be enabled to successfully use of the breadth of claimed SPARC/osteonectin antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules such as those claimed in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

4. Claims 55-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in the written description rejection of claims 15-17, 39-42 and 44-54 under 35 USC § 112 set forth in the Official Action mailed 3-10-03.

5. Applicant's arguments filed 8-25-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification as filed conveys to those skilled in the art that Applicants were in possession of the claimed invention at the time of filing. However, Applicants do not point to any portion of the specification as filed that would clearly predict the structure of functional antisense nucleic acid molecules that are useful in the claimed methods. With the exception of the antisense nucleic acid molecule that is the reverse complement of nucleotides 15 to 1689 of SPARC cDNA, there are no other examples of functional antisense nucleic acid molecules that would be useful in the claimed methods.

As stated in the prior Office Action, according to MPEP § 2163 "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

One of skill in the art would not have been able to readily envisage a representative number of antisense nucleic acid molecules that bind to SEQ ID NO: 1 and function to prevent or decrease expression of human osteonectin, without the need for further experimentation.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

SEAN McGARRY
PRIMARY EXAMINER

Janet L. Epps-Ford, Ph.D.
Examiner